PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/005461	17.02.2005	17.02.2004

International Patent Classification (IPC) or both national classification and IPC
C12N15/869, C12N15/86, A61K48/00, C12N5/10

Applicant
UNIVERSITY OF FLORIDA RESEARCH FOUNDATION, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/005461

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-45, 53-71
	No:	Claims	46-52
Inventive step (IS)	Yes:	Claims	none
	No:	Claims	1-71
Industrial applicability (IA)	Yes:	Claims	1-70
	No:	Claims	no opinion: 71

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1) The Application

The present application is based on the isolation of insulator/boundary regions from the LAT (latency associated transcript) region of Herpes simplex virus 1. These regions are combined with a LAT enhancer element and LAP1 promoter into an expression cassette. The insulator/boundary regions are useful in maintaining long-term expression of therapeutic genes, by preventing inactivation of transcription.

2) The Prior Art

Reference is made to the following document/s/:

D1: WO 98/30707 A (UNIVERSITY COLLEGE LONDON; COFFIN, ROBERT, STUART; LATCHMAN, DAVID, SE) 16 July 1998 (1998-07-16)

D2: PALMER J A ET AL: "Development and optimization of herpes simplex virus vectors for multiple long-term delivery to the peripheral nervous system" JOURNAL OF VIROLOGY, THE AMERICAN SOCIETY FOR MICROBIOLOGY, US, vol. 74, no. 12, June 2000 (2000-06), pages 5604-5618, XP002164866 ISSN: 0022-538X

D3: LACHMANN R H ET AL: "UTILIZATION OF THE HERPES SIMPLEX VIRUS TYPE 1 LATENCY-ASSOCIATED REGULATORY REGION TO DRIVE STABLE REPORTER GENE EXPRESSION IN THE NERVOUS SYSTEM" JOURNAL OF VIROLOGY, THE AMERICAN SOCIETY FOR MICROBIOLOGY, US, vol. 71, no. 4, April 1997 (1997-04), pages 3197-3207, XP000654376 ISSN: 0022-538X

D4: PERNG GUEY-CHUEN ET AL: "The spontaneous reactivation function of the herpes simplex virus type 1 LAT gene resides completely within the first 1.5 kilobases of the 8.3-kilobase primary transcript" JOURNAL OF VIROLOGY, vol. 70, no. 2, 1996, pages 976-984, XP002336979 ISSN: 0022-538X

D5: WEST A G ET AL: "Insulators: Many functions, many mechanisms" GENES AND DEVELOPMENT, COLD SPRING HARBOR LABORATORY PRESS, NEW YORK, US, vol. 16, no. 3, 1 February 2002 (2002-02-01), pages 271-288, XP002249349 ISSN: 0890-9369

D6: BERTHOMME HERVE ET AL: "Evidence for a bidirectional element located downstream from the herpes simple virus type 1 latency-associated promoter that increases its

activity during latency" JOURNAL OF VIROLOGY, vol. 74, no. 8, April 2000 (2000-04), pages 3613-3622, XP002336980 ISSN: 0022-538X

3) Novelty

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 46 to 52 is not new in the sense of Article 33(2) PCT.

D1, D2 and D3 each disclose the construction of expression cassettes comprising elements of the LAT region of HSV1 as well as mammalian promoters and heterologous genes. Said cassettes are introduced into the LAT region of the viral genome by homologous recombination. Thus, it is considered that the virions comprise said cassettes within the LAT region of their genome. Such a recombinant virus genome comprises HSV LAT enhancer elements flanked by insulators and the promoter LAP1 as well as a mammalian promoter. Virions and viral particles as well as the transfected cells as disclosed by D1 to D3 are considered novelty destroying to claims 46 to 52.

4) Inventive Step

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 to 45 and 53 to 71 does not involve an inventive step in the sense of Article 33(3) PCT.

4.1 In view of above discussed lack of novelty of the virions, viral particles and host cells, the subject-matter of claims 53 to 71 based thereon cannot be considered inventive, because the claims do not provide any additional features justifying an inventive step.

4.2 Claims 1 to 39 are directed to an isolated polynucleotide comprising certain elements of the HSV LAT region.

The document D1 is regarded as being the closest prior art to the subject-matter of claim 1 and discloses the introduction of heterologous promoters and genes into the LAT region of HSV.

4.3 The problem to be solved by the present invention may be regarded as the provision of expression cassettes allowing the efficient long-term expression of therapeutic genes. This problem was solved by the isolation of specific insulator/boundary regions of LAT which are placed upstream and downstream of the LAT elements combined with the gene to be expressed.

4.4 The solution to this problem proposed by the present application is considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

A LAT enhancer element and the promoters LAP1 and LAP2 are known in the art. However, although the LAT region had been used to express heterologous genes, long-term expression during latency was described to declined after a certain time period (D6).

Although it was suggested that there appears to be an upstream regulatory element allowing long-term expression of genes during latency of HSV-1 (D4) no insulator- type element had been identified. Insulator regions had been described for a number of eukaryotic genes (D5). Nevertheless, it does not appear obvious from the prior art to search for regulatory regions of insulator-type within the LAT region and to combine these with the already known LAT regulatory elements and promoters.

4.5 However, this solution is only represented by partial claims combining the features of claim 8, 16, 21, 26, 27 to 29 and 30. Only a polynucleotide according to claim 30 referring back to all said claims in combination could be considered as inventive, provided the essential elements were clearly defined (see also Item VIII). Same applies to claims 40 and 45 directed to a vector based on such a polynucleotide, as well as to dependent claims 31 to 39 and 42 to 44.

5) Industrial Applicability

Claim 71 may be understood as method of medical treatment or diagnosis.

For the assessment of said claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

The following document was cited in the international search report as PAX document and may be relevant to any claimed subject-matter not entitled to the priority.

CABBED NICOLE J ET AL: "The herpes simplex virus type 1 latency-associated transcript (LAT) enhancer/RC is hyper acetylated during latency independently of LAT transcription" JOURNAL OF VIROLOGY, vol. 78, no. 22, November 2004 (2004-11), pages 12508-12518, XP002336981 ISSN: 0022-538X

Re Item VIII

Certain observations on the international application

The application does not meet the requirements of Article 6 PCT, because claims 1 to 39, 41, 44, 49 and 50 are not clear.

The elements of the polynucleotide are only defined by vague designations ("LAT insulatory/boundary region", "LAT enhancer element" see claims 1 to 4, 9 to 12, 17, 22, 27 to 30) or by an unclear numbering of positions referring either to the HSV exons, to HSV elements or to positions of the HSV1 genome (see claims 5 to 8, 13 to 16, 18 to 21, 23 to 26). Without a precise definition of the elements and their positions it is not apparent how the claimed polynucleotide actually differs from the genomic DNA obtainable from native HSV1 or of recombinant HSV disclosed by D1 to D3.

Arbitrary designations such as "insulated Viral Artificial Chromosome vector" or "pIVAC_1.0" (see) render the scope of claims 41 and 44 unclear.

It is not clear, what is meant by the term "a plurality of viral particles" in claims 49 and 50.